II. REQUEST FOR RECONSIDERATION UNDER 37 C.F.R. §1.111

A. Status of the Claims

Applicants elected Group I claim, claims 1-32, in a Response to Restriction Requirement mailed in the case on November 12, 2001, which were the subject of the instant Office Action. Claim 30 has been amended herein. The amendment does not change the scope of the claim and accordingly Applicants do not intend to disclaim any subject matter by the amendment. Claims 1-32 are presented herein for reconsideration.

B. Status of the Specification

1.) The Action indicates that page 31 of the Specification has been torn and a part of the narrative is missing. In response, Applicants note that a duplicate copy of page 31 as originally filed with the application has been submitted herewith.

2.) The Action objects to the specification for the recitation of "Escherichia coli" without italicizing the term. In response, Applicants note that the specification has been amended to italicize the referenced term. Removal of the objection is therefore respectfully requested.

3.) The Action objects to the specification for the use of worldwide web addresses on pages 52 and 62. It is stated that the worldwide web addresses must be deleted. In response, Applicants note that Applicants are not prohibited from including worldwide web addresses *per se*. As set forth in MPEP § 608.01, Applicants are only prohibited from including hyperlinks and other forms of browser-executable codes, notably a URL placed between the symbols "<" and ">" and "http://" followed by an URL address. The worldwide web address on page 52 does not meet this criteria, and thus is not properly objected to. The worldwide web address on page 62

has been amended to a non-executable form. As such, it is believed that the objection is now moot and removal thereof is respectfully requested.

C. Claim Objection

The Action objects to claims 30 because it recites "FACS," instead of the full term for which this acronym stands, "Fluorescence Activated Cell Sorting." In response, Applicants note that the recited term has been amended to give the full name for the term. Removal of the objection is thus respectfully requested.

D. Drawings

The Action notes that the drawings have been objected to by the draftsman under 37 C.F.R. 1.84 or 1.152. In response, Applicants note that formal drawings will be submitted upon the indication of otherwise allowable subject matter.

E. Rejection of Claims Under 35 U.S.C. §112, Second Paragraph

The Action rejects claims 1, 2, 4, 7, 13 and 22 under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out the subject matter which Applicant regards as the invention. In particular, the Action alleges that the term "capable of" cannot be ascertained. Applicants respectfully traverse.

The term "capable" has a meaning that is well known to those of skill in the art and thus the use of the term in the claims is not indefinite. The term "capable of" is understood to those of skill in the art to mean having the ability to complete a specified task or function. For example, the relevant definition of the term "capable" from the online version of the Encarta™

dictionary (http://dictionary.msn.com/) is given as "able to do particular thing: possessing the qualities needed to do a particular thing." Appendix C. The relevant definition from the online version of the Merriam-Webster's Collegiate Dictionary (http://www.m-w.com/cgi-bin/dictionary) is given as "having attributes (as physical or mental power) required for performance or accomplishment." Appendix D.

In claim 1, the term "capable of" is used twice. First, the term "capable of binding a target ligand" is used and, second, the term "capable of diffusing into said bacterium" is used. Given the well known meaning of the term "capable" and the derivative thereof "capable of", the meaning of these terms as they are used in the claim is definite. Thus a binding protein "capable of binding a target ligand" refers to a binding protein having the ability to bind a target ligand. Similarly, a labeled ligand "capable of diffusing into said bacterium" refers to a labeled ligand having the ability to diffuse into the referenced bacterium. Further, as claim 1 specifies that the ligand and the binding protein are bound in the bacterium, one of skill in the art will recognize that "capable of binding" requires the capability of binding in the bacterial periplasm. The meaning of the terms are thus readily understood by one of skill in the art and are not indefinite.

Claim 4 also refers to a leader sequence that is "capable of directing expression of said candidate binding protein in said periplasm." Once again, this term is not indefinite as whether a leader sequence has the ability to direct the expression of a candidate binding protein in the periplasm is readily ascertainable and understood by one of skill in the art. The use of "capable of" in the remaining rejected claims is thus not indefinite as described herein above for the same reason, because "capable of" is a readily ascertainable standard well known to hose of skill in the art.

The second paragraph of 35 U.S.C. §112 requires only that it be clear to those skilled in the art what Applicant intends to claim. What is dispositive is whether one of ordinary skill in the art would understand what is claimed when the claims are read in light of the specification. Where, as here, one of skill would readily understand the meaning of a given term, the use of that term in the claims is not indefinite.

In light of the foregoing, Applicant hereby respectfully requests that the rejection of claims 1, 2, 4, 7, 13 and 22 under 35 U.S.C. §112, second paragraph, be withdrawn.

E. Rejections Under 35 U.S.C. §102(b)

The Action rejects claims 1-32 under 35 U.S.C. §102(b) as anticipated by, individually, Iverson *et al.* (WO 98/49286) and Georgiou *et al.* (U.S. Patent No. 5,866,344). Applicants respectfully traverse as set forth below.

1.) The Action first rejects claims 1-32 under 35 U.S.C. §102(b) as anticipated by Iverson *et al.* (WO 98/49286). Applicants respectfully traverse as the cited reference does not teach the claimed method. Claim 1 of the instant case, upon which each of the remaining rejected claims depends, reads as follows:

> 1. A method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of binding a target ligand comprising the steps of:
> (a) providing a Gram negative bacterium comprising a nucleic acid sequence encoding a candidate binding protein, wherein said binding protein is expressed in soluble form in said bacterium;
> (b) contacting said bacterium with a labeled ligand capable of diffusing into said bacterium; and
> (c) selecting said bacterium based on the presence of said labeled ligand within the bacterium, wherein said ligand and said candidate binding protein are bound in said bacterium.

The Action has not alleged teachings of the cited reference showing any of steps (a) – (c) nor a basis for concluding that such steps can be found in the reference. For example, step (a) of claim 1 entails providing a Gram negative bacterium expressing a binding protein in soluble form. The Action alleges that Iverson teaches *cell-surface* expression, but not expression in the periplasm. Similarly, step (b) entails contacting the bacterium with a labeled ligand capable of diffusing into the bacterium. Again, no teaching of Iverson has been alleged indicating contacting a gram negative bacterium with a labeled ligand capable of diffusing into the bacterium. Finally, step (c) of claim 1 entails "selecting said bacterium based on the presence of said labeled ligand within the bacterium, wherein said ligand and said candidate binding protein are bound in said bacterium." The Action, however, alleges identification of *cell surface*-bound ligands, but not "based on the presence of said labeled ligand within the bacterium" or wherein "said ligand and said candidate binding protein are bound in said bacterium."

Therefore, the Action does not show all steps of the claimed invention can be found in the prior art. To the extent that inherency is relied upon as the basis for the rejection, it is noted that a rationale or evidence tending to show the alleged inherency must be provided. *In re Oelrich*, 666 F.2d 578, 581-582 (CCPA 1981). No such basis has been provided. Removal of the rejection is thus respectfully requested.

2.) The Action rejects claims 1-32 under 35 U.S.C. §102(b) as anticipated by Georgiou *et al.* (U.S. Patent No. 5,866,344). Applicants respectfully traverse as the reference does not teach the claimed method. The Action alleges that Georgiou *et al.* teaches *cell surface* expression of antigen antibodies, but does not allege that the reference teaches expression of a binding protein in soluble form in a bacterium. Further, it is not alleged that the reference

teaches contacting a gram negative bacterium with a labeled ligand capable of diffusing into the bacterium. Finally, it is not alleged the reference teaches selecting a bacterium based on the presence of labeled ligand within the bacterium, wherein the ligand and a candidate binding protein are bound in the bacterium." Absent such teaching of the claim limitations or such a rationale to conclude that such a teaching has been made, the reference cannot anticipate the claims. Removal of the rejection is thus respectfully requested.

G. Rejections Under 35 U.S.C. §103(a)

The Action rejects claim 26 under 35 U.S.C. §103 as allegedly being obvious over Iverson *et al.* (WO 98/49286) or Georgiou (U.S. Patent No. 5,866,344) in view of Pini *et al.* (J. Biol. Chem., 1998, Vol. 283, No. 34, p. 21769-21776). Applicants respectfully traverse.

It is first noted that claim 26 depends, by way of dependency from claims 24 and 25, from claim 1. Accordingly, the claim includes all of the limitations of claim 1 and is fully patentable over the prior art as set forth above. 35 U.S.C. §112, fourth paragraph. In this regard, establishment of a prima facie case of obviousness requires that the prior art teach or suggest all claim limitations, provide a motivation or suggestion to combine the references to arrive at the invention and provide a reasonable expectation of success in making the combination. *See In re Vaeck*, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991), *see also*, M.P.E.P. § 2142. No such showing has been made. Pini *et al.* is alleged in the Action to teach use of phage in constructing antibody libraries and certain advantages of phage antibody display. However, it is not alleged that Pini *et al.* remedies any of the deficiencies described herein above with respect to claim 1. Absent a showing of such a teaching, the claims cannot be rendered obvious. Still further, there could not have been an expectation of success to arrive at the invention with out a teaching of all

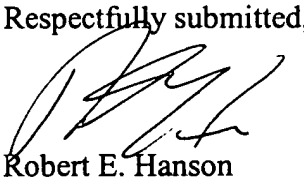
elements of the claimed invention, let alone the motivation to do so. As such, the cited prior art does not render the claimed invention obvious.

Removal of the rejection under 35 U.S.C. §103 is thus respectfully requested.

H. Conclusion

In light of the foregoing, applicants submit that all claims are in condition for allowance, and an early indication to that effect is earnestly solicited. The examiner is invited to contact the undersigned (512)536-3085 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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Date: July 12, 2002

APPENDIX A: MARKED UP COPY OF AMENDMENTS

In the Specification:

Please replace the paragraph at page 13, lines 11-20 with the following:

--The present technology circumvents the limitations of the prior art and provides an entire[t]ly novel means for the screening of very large polypeptide libraries. In particular, the invention overcomes deficiencies in the prior art by providing a rapid approach for isolating proteins that bind to small molecules and peptides via "display-less" library screening. A description of an example of such a process in accordance with the invention is described for illustrative purposes in FIG. 1. In the technique, libraries of candidate binding proteins, such as antibody sequences, are expressed in soluble form in the periplasmic space of gram negative bacteria, such as *Escherichia coli* [Escherichia coli], and are mixed with a labeled ligand. The periplasm comprises the space defined by the inner and outer membranes of a gram-negative bacterium.--

Please replace the paragraph at page 62, lines 14-28 with the following:

--This example summarizes the screening of a repertoire antibody library to the ligand TNB (trinitrobenzene). Library screening was initiated by first carrying out three rounds of phage panning of a repertoire library (Griffin –1 library) using standard protocols (see example 6, also described in [http://www.mrc-cpe.cam.ac.uk/~phage/g1p.html] www.mrc-cpe.cam.ac.uk/~phage/g1p.html). Phage rescued from various rounds of panning were used to infect the *E. coli* ABLE C. The cells were grown to mid-exponential phase, induced for expression of scFv antibodies as described above and labeled with 100 nM TNBS conjugated to the fluorescent dye Cy5. The labeled cells were analyzed by flow cytometry using a Cytomation MoFlo instrument equipped with a 5 mM diode laser emitting at 633 nm. Highly fluorescent clones were isolated on membrane filters and analyzed further. Three out of 10 clones isolated by FACS were analyzed further and found to exhibit strong binding to a TNBS-BSA conjugate. Sequence analysis confirmed that one of the TNBS specific clones had also been found by phage display. However, the two other clones isolated by the present invention (periplasmic expression of the library and FACS screening) did not correspond to any of the clones isolated by phage panning.--

In the Claims:

Please amend claim 30 as indicated below:

30. (Amended) The method of claim 1, wherein said selecting comprises fluorescent activated cell sorting [FACS].

APPENDIX B: CLEAN COPY OF CLAIMS

1. A method of obtaining a bacterium comprising a nucleic acid sequence encoding a binding protein capable of binding a target ligand comprising the steps of:

(a) providing a Gram negative bacterium comprising a nucleic acid sequence encoding a candidate binding protein, wherein said binding protein is expressed in soluble form in said bacterium;

(b) contacting said bacterium with a labeled ligand capable of diffusing into said bacterium; and

(c) selecting said bacterium based on the presence of said labeled ligand within the bacterium, wherein said ligand and said candidate binding protein are bound in said bacterium.

2. The method of claim 1, further defined as a method of obtaining a nucleic acid sequence encoding a binding protein capable of binding a target ligand, the method further comprising the step of:

(d) cloning said nucleic acid sequence encoding said candidate binding protein.

3. The method of claim 1, wherein said binding protein is expressed in soluble form in the periplasm of said bacterium.

4. The method of claim 3, wherein said nucleic acid sequence encoding a candidate binding protein is further defined as operably linked to a leader sequence capable of directing expression of said candidate binding protein in said periplasm.

5. The method of claim 1, wherein said Gram negative bacterium is an *E. coli* bacterium.

6. The method of claim 1, further defined as comprising providing a population of Gram negative bacteria.

7. The method of claim 6, wherein said population of bacteria is further defined as collectively capable of expressing a plurality of candidate binding proteins.

8. The method of claim 7, wherein said population of bacteria is obtained by a method comprising the steps of:

(a) preparing a plurality DNA inserts which collectively encode a plurality of different potential binding proteins, and

(b) transforming a population of Gram negative bacteria with said DNA inserts.

9. The method of claim 6, wherein said population of Gram negative bacteria is contacted with said labeled ligand.

10. The method of claim 1, wherein said candidate binding protein is further defined as an antibody or fragment thereof.

11. The method of claim 1, wherein said candidate binding protein is further defined as a binding protein other than an antibody.

12. The method of claim 1, wherein said candidate binding protein is further defined as an enzyme.

13. The method of claim 1, wherein said candidate binding protein is further defined as not capable of diffusing out of said periplasm in intact bacteria.

14. The method of claim 1, wherein said labeled ligand comprises a peptide.

15. The method of claim 1, wherein said labeled ligand comprises a polypeptide.

16. The method of claim 1, wherein said labeled ligand comprises an enzyme.

17. The method of claim 1 where said labeled ligand comprises a nucleic acid.

18. The method of claim 1, wherein said labeled ligand is further defined as comprising a molecular weight of less than about 20,000 Da.

19. The method of claim 1, wherein said labeled ligand is further defined as comprising a molecular weight of less than about 5,000 Da.

20. The method of claim 1, wherein said labeled ligand is further defined as comprising a molecular weight of greater than 600 Da and less than about 30,000 Da.

21. The method of claim 1, wherein said labeled ligand is further defined as fluorescently labeled.

22. The methods of claim 1, wherein said nucleic acid encoding a candidate binding protein if further defined as capable of being amplified following said selection.

23. The method of claim 1, further comprising treating said bacterium to facilitate said diffusing into said periplasm.

24. The method of claim 23, comprising treating the bacterium with hyperosmotic conditions.

25. The method of claim 23, comprising treating the bacterium with physical stress.

26. The method of claim 24, comprising treating the bacterium with a phage.

27. The method of claim 1, wherein said bacterium is grown at a sub-physiological temperature.

28. The method of claim 27, wherein said sub-physiological temperature is about 25°C

29. The method of claim 1, further comprising removing labeled ligand not bound to said candidate binding protein.

30. The method of claim 1, wherein said selecting comprises fluorescent activated cell sorting.

31. The method of claim 1, wherein said selecting comprises magnetic separation.

32. The method of claim 1, wherein said ligand and said candidate binding protein are reversibly bound in said periplasm.

Word List

Previous Next

cap
CAP
cap.
capability
Capablanca, José Raúl
capable
capably
capacious
capacitance
capacitate
capacitation
capacitive
capacitor
capacity
capacity configuration

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capable

WAV AIFF **Hear this word spoken**
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ca·pa·ble [káypəb'l] *adjective*

1. **doing something well:** good at a particular task or job or at a number of different things • *a very capable hotel manager*

2. **able to do particular thing:** possessing the qualities needed to do a particular thing

3. **liable to:** permitting or susceptible to something • *an action capable of being misinterpreted*

4. LAW **legally competent:** the ability or the legal power to do something

[Mid-16th century. Via French from late Latin *capabilis* , from Latin *capere* "to take." Originally "able to take in."]

•ca·pa·ble·ness *noun*

See a pronunciation key

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- C mpany Info
- Customer Service
- Network Options
- Language Zone
- Th Lighter Side
- Sit Map

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2 entries found for **CAPABLE**.
To select an entry, click on it.

capable
capable de tout
Go

Main Entry: **ca·pa·ble**
Pronunciation: 'kA-p&-b&l, *in rapid speech* 'kAp-b&l
Function: *adjective*
Etymology: Middle French or Late Latin; Middle French *capable*, from Late Latin *capabilis*, irregular from Latin *capere* to take -- more at HEAVE
Date: 1579
1 : **SUSCEPTIBLE** <a remark *capable* of being misunderstood>
2 *obsolete* **:** **COMPREHENSIVE**
3 : having attributes (as physical or mental power) required for performance or accomplishment <is *capable* of intense concentration>
4 : having traits conducive to or features permitting <this woman is *capable* of murder by violence -- Robert Graves> <an outer coat of light color *capable* of reflecting solar heat -- *Current Biography*>
5 : having legal right to own, enjoy, or perform
6 : having general efficiency and ability
- **ca·pa·ble·ness** /'kA-p&-b&l-n&s/ *noun*
- **ca·pa·bly** /-p&-blE/ *adverb*

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Pronunciation Symbols

\&\ as **a** and **u** in **abut**	\e\ as **e** in **bet**	\o\ as **aw** in **law**
\ᵊ\ as **e** in **kitten**	\E\ as **ea** in **easy**	\oi\ as **oy** in **boy**
\&r\ as **ur/er** in **further**	\g\ as **g** in **go**	\th\ as **th** in **thin**
\a\ as **a** in **ash**	\i\ as **i** in **hit**	\[th]\ as **th** in **the**
\A\ as **a** in **ace**	\I\ as **i** in **ice**	\ü\ as **oo** in **loot**
\ä\ as **o** in **mop**	\j\ as **j** in **job**	\u\ as **oo** in **foot**
\au\ as **ou** in **out**	\[ng]\ as **ng** in **sing**	\y\ as **y** in **yet**
\ch\ as **ch** in **chin**	\O\ as **o** in **go**	\zh\ as **si** in **vision**

For more information see the Guide To Pronunciation.

herein by reference), including microinjection (Harlan and Weintraub, 1985; U.S. Patent 5,789,215, incorporated herein by reference); by electroporation (U.S. Patent 5,384,253, incorporated herein by reference); by calcium phosphate precipitation (Graham and Van Der Eb, 1973; Chen and Okayama, 1987; Rippe *et al.*, 1990); by using DEAE-dextran followed by polyethylene glycol (Gopal, 1985); by direct sonic loading (Fechheimer *et al.*, 1987); by liposome mediated transfection (Nicolau and Sene, 1982; Fraley *et al.*, 1979; Nicolau *et al.*, 1987; Wong *et al.*, 1980; Kaneda *et al.*, 1989; Kato *et al.*, 1991); by microprojectile bombardment (PCT Application Nos. WO 94/09699 and 95/06128; U.S. Patents 5,610,042; 5,322,783 5,563,055, 5,550,318, 5,538,877 and 5,538,880, and each incorporated herein by reference); by agitation with silicon carbide fibers (Kaeppler *et al.*, 1990; U.S. Patents 5,302,523 and 5,464,765, each incorporated herein by reference); by *Agrobacterium*-mediated transformation (U.S. Patents 5,591,616 and 5,563,055, each incorporated herein by reference); or by PEG-mediated transformation of protoplasts (Omirulleh *et al.*, 1993; U.S. Patents 4,684,611 and 4,952,500, each incorporated herein by reference); by desiccation/inhibition-mediated DNA uptake (Potrykus *et al.*, 1985). Through the application of techniques such as these, organelle(s), cell(s), tissue(s) or organism(s) may be stably or transiently transformed.

a. Electroporation

In certain embodiments of the present invention, a nucleic acid is introduced into a cell *via* electroporation. Electroporation involves the exposure of a suspension of cells and DNA to a high-voltage electric discharge. In some variants of this method, certain cell wall-degrading enzymes, such as pectin-degrading enzymes, are employed to render the target recipient cells more susceptible to transformation by electroporation than untreated cells (U.S. Patent 5,384,253, incorporated herein by reference). Alternatively, recipient cells can be made more susceptible to transformation by mechanical wounding.

b. Calcium Phosphate

In other embodiments of the present invention, a nucleic acid is introduced to the cells using calcium phosphate precipitation. Human KB cells have been transfected with adenovirus 5 DNA (Graham and Van Der Eb, 1973) using this technique. Also in this